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The Flavor and Fragrance High Production Volume Consortia (FFHPVC)

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Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue N.W.
Washington, D.C. 20460

Dear Administrator:

On behalf of the Flavor and Fragrance High Production Volume Consortia, I wish to thank the Environmental Protection Agency (EPA) for their comments on the test plan and robust summaries on the Chemical Category "C6-C10 Aliphatic Aldehydes and Carboxylic Acids". The C-6 to C-10 Consortium, as a member of FFHPVC, serves as an industry consortium to coordinate testing activities for terpenoid substances under the Chemical Right-to-Know Program. Since 1999, the four (4) companies that are current members of C-6 to C-10 Consortium have supported the collection and review of available test data, development of test plans and robust summaries for each of the sponsored chemicals, and conducted additional testing.

Based on our initial recommendations for testing and the peer-reviewed comments of the EPA, the C-6 to C-10 Consortium of the Flavor and Fragrance High Production Volume Consortia (FFHPVC) is pleased to revise the name of the category to "C7-C9 Aliphatic Aldehydes and Carboxylic Acids" and submit the following revised test plan and robust summaries for the chemical category. The revised test plan and robust summaries contain the results of additional toxicity studies and additional metabolic information that addresses the questions and comments made by the EPA in its letter dated 12/11/2001. This letter contains responses to the comments made by the EPA . These responses taken together with the inclusion of new study data and other information constitute the key changes to the original test plan and robust summaries.

Based on this additional information, the Consortium concludes that the experimental and model data for physiochemical properties, environmental fate, ecotoxicity, and human health endpoints are consistent for all members of this chemical category. The database of information on category

members permits one to reliably predict endpoint values for other untested members of the category. Therefore, these data support the inclusion of the four listed substances in the chemical category and would allow for other structurally related substances to be included in the chemical category.

As is the case for the majority of chemical categories sponsored by FFHPVC, the group of aliphatic aldehydes and acids are regulated by the U.S. Food and Drug Administration (FDA) as flavouring agents permitted to be used in food. Most of the physiochemical and human health assessment data have been provided to the FDA and the World Health Organization during their evaluation of these substances as food additives. The three aldehydes and one carboxylic acid that constitute the members of this chemical category have been reviewed by the World Health Organization/Food and Agriculture Organization Joint Expert Committee for the Evaluation of Food Additives (WHO/FAO JECFA) for use as flavoring substances in food. As part of its responsibility, JECFA maintains on ongoing program of review of the safety of food additives (WHO Technical Series Nos. 38, 40, 42, 44, 46, and 48). In 1997, these four substances [WHO Food Additive Series: 40, 1998; see Revised Test Plan] were recognized as safe for use in food.

The substances in this category are also recognized as “Generally Recognized as Safe” (GRAS) for their intended use in food by the United States Food and Drug Administration under the Code of Federal Regulations (CFR 172.515). Under supervision of the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences, specifications for the commercial use of each of these substances in food are published in the Food Chemical Codex [FFC, 1996; see Revised Test Plan].

Based on the long history of use of these substances both as naturally occurring components of food and as substances intentionally added to food, the hazard assessments performed by the US FDA and WHO/FAO JECFA, and the current regulatory status for the addition of these substances to the food supply, there is no compelling evidence that these substances should be further tested for physiochemical properties and human health endpoints in the EPA Chemical “Right to Know” Program. We do, however, maintain that data on the environmental fate and ecotoxicity are relevant to the HPV Challenge program.

We consider that the test plan and robust summaries for this category are final and have no plans to provide additional data. Your comprehensive comments provided the necessary guidance to complete the test plan and robust summaries for this category. The collaboration between the C7-C9 Consortium and the Environmental Protection Agency in the Chemical “Right to Know” Program has produced a hazard database that will be useful to the public for decades to come. Thank you for the opportunity to participate in such a program.

If you have any questions or comments concerning the contents of this letter, please feel free to contact me at any time (202-331-2325) or tadams@therobertsgroup.net.

Best regards,

Timothy B. Adams, Ph.D.
Technical Contact Person for FFHPVC

Highlights of the Revision of the Test Plan and Robust Summaries for the "C7-C9 Linear Aliphatic AIdehydes and Carboxylic Acids.

1. Revision of the metabolism to include the metabolic fate of branched-chain aldehydes and carboxylic acids
2. Biodegradation studies on pentanoic acid, heptanoic acid, and nonanoic acid
3. Fugacity determinations for all members of the chemical category using EQC Fugacity Model III
4. OECD 202 guideline studies of the toxicity of heptanal and nonanal to *Daphnia magna*.
5. OECD 20 guideline studies of the toxicity of heptanal and nonanal to green algae.

SUMMARY OF EPA COMMENTS The sponsor, the C6-C10 Consortium of the Flavorings and Fragrances High Production Volume Consortia, submitted a test plan and robust summaries to EPA for C6-C10 Aliphatic Aldehydes and Carboxylic Acids. EPA posted the submission on the ChemRTK website on 21 June 2001.

EPA has reviewed this submission and reached the following conclusions:

1. Category Justification. The justification for grouping three straight-chain aldehydes and a carboxylic acid (heptanoic acid) appears appropriate. However, using analog data on 2,6-dimethyl-5-heptenal to support the category is not adequately justified for health effects endpoints. Additional information is needed on how a branched aldehyde is a suitable analog; for example, whether its metabolism is similar to that of other members of the category.

The test plan has been revised to include extensive data on the metabolism of alkyl-substituted alcohols, aldehydes, and carboxylic acids. The data demonstrate that these substances which include branched chain aliphatic alcohols, aldehydes and acids that are endogenous intermediary amino acid metabolites enter the β-oxidation pathway (see revised test plan).

2. Physicochemical and Environmental Fate Data. EPA agrees with the category approach and test plan for these endpoints.

3. Health Endpoints. The health effects data were adequate for acute toxicity, genetic toxicity, and developmental toxicity endpoints. The data for reproductive toxicity endpoints are adequate for the shorter-chain members of the category and these results can reasonably be extrapolated to the longer-chained members of the category. For the repeated-dose toxicity endpoint, data on an analog are used; additional information is needed to justify its use.

Data on the analog is provided in the revised test plan.

4. Ecological Effects. The measured environmental effects data for heptanal appear adequate and agree with ECOSAR predictions. EPA agrees with the proposed testing of nonanal in daphnia and algae.

EPA requests that the Submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON C6-C10 ALIPHATIC ALDEHYDES AND CARBOXYLIC ACIDS CATEGORY CHALLENGE SUBMISSION

Category Definition

The Submitter has defined the C6-C10 Aliphatic Aldehydes and Carboxylic Acids category as ". . . a homologous series of straight chained saturated aldehydes of carbon chain lengths C7 to C9, heptanal, octanal, nonanal and one structurally related carboxylic acid, heptanoic acid."

It is unclear why the category is named "C6-C10 Aliphatic Aldehydes and Carboxylic Acids" when the chemicals discussed in the test plan contain carbon chain lengths of C7 to C9. Although data for hexanal and decanal support the category and the sponsor is the C6-C10 Consortium, the category name should reflect the range of chemicals in it.

The category name has been changed to reflect the chain length of the substances in the chemical category. The category will be named “C7-C9 Aliphatic Aldehydes and Carboxylic Acids”.

Category Justification

The rationale for grouping C6-C10 Aliphatic Aldehydes and Carboxylic Acids is based on their close structural similarities, physicochemical properties, and their metabolic fate. As this group represents a homologous series and the structural similarities of the aldehydes are clear, it is anticipated that the aldehydes in this category will show regular physicochemical property trends.

The Submitter describes the in vivo metabolic pathways for the linear, short-chain aldehydes and their corresponding carboxylic acids. This description appears to support the contention that (1) aldehydes are easily oxidized to their respective carboxylic acid derivatives in a number of environmental settings; (2) enzymatic pathways common to a number of organisms efficiently oxidize aldehydes to the corresponding carboxylic acids in vivo; and (3) once converted, these carboxylic acids can be metabolized to carbon dioxide through catabolism and participation in the tricarboxylic acid cycle or assimilated into other biomolecules through the fatty acid pathway.

The Submitter has used data for 2,6-dimethyl-5-heptenal to support the category. No information is presented in the test plan on the metabolism of the 2,6-dimethyl-5-heptenal. If the metabolic pathway for this chemical is similar to that of the straight-chain aldehydes, then its use as an analog is acceptable.

For ecological effects, the category approach appears to be appropriately based on structure-activity relationships and consistency between the measured and predicted data.

The metabolic data to support the inclusion of data for the branched-chain aldehyde has been includedin the test plan.

Test Plan

Chemistry *(melting point, boiling point, vapor pressure, water solubility, and partition coefficient).*

The submitted physicochemical data appear adequate.

Environmental Fate (*photodegradation, stability in water, biodegradation, and transport/distribution)*.

Octanol/Water Partition Coefficient. EPA agrees with the submitter’s approach. *Water Solubility*. On page 8 of the Test Plan, the submitter reported a literature value of 242 mg/L at 15 °C [Merck, 1997] for heptanoic acid. However, the Merck Index (1996, Twelfth edition, page 797) reports a value of 0.2419 g/100ml at 15 °C, which is equal to 2419 mg/L. The submitter should correct this discrepancy.

This data for the water solubility has been reconciled in the test plan and robust summaries.

Chemical Transport and Distribution in the Environment. The submitter’s approach to the environmental fate endpoints is generally acceptable. The submitter has used EQC Fugacity Level I model. However, EPA recommends using the EQC Fugacity Level III model from the Canadian Environment Modeling Centre at Trent University, found at the following Web address: http://www.trentu.ca/academic/aminss/envmodel. A Fugacity Level III model is more realistic and useful for estimating a chemical’s fate in the environment.

Fugacity Level III Model data has been included in the revised test plan and robust summaries.

Biodegradation. The submitted data are adequate for the purposes of the HPV Challenge Program. EPA also agrees with the submitter's plan to test heptanoic acid for its biodegradation potential.

Biodegradation data for heptanoic acid, pentanoic acid, and nonanoic acid have been included in the robust summary and test plan. These data indicate the homologous series of acid is readily biodegradable.

Health Effects *(acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).*

The submitter presented a number of studies that adequately address the potential toxicity of heptanoic acid. In several instances for the aldehydes in the category (heptanal, octanal, and nonanal), hexanal, 2,6-dimethyl-5-heptenal, and a mixture of C8-C12 aldehydes were used as analogs. Hexanal is an acceptable analog based on its structural similarity to the category members. The use of 2,6-dimethyl-5-heptenal as an analog is acceptable (see category justification), if its metabolic pathway is similar to those of the straight-chain aldehydes/carboxylic acids (ß-oxidation). This is not discussed in the test plan. Finally, a mixture of C8-C12 aldehydes (incompletely characterized–it is unclear if branched aldehydes are present) is used in one repeated dose toxicity study; this study is considered inadequate. However, adequate repeated-dose toxicity studies on hexanal and 2,6-dimethyl-5-heptenal satisfy this endpoint, pending additional information. EPA recommends that to the extent that their inclusion can be justified, the final category analysis should include data for hexanal and 2,6-dimethyl-5-heptenal as entries in the category data matrix.

Repeated Dose Toxicity. Of the oral studies representing the aldehyde toxicities, one that used hexanal, and two that used 2,6-dimethyl-5-heptenal appear adequate. However, as stated in the above paragraph, the sponsor should provide additional information on the metabolism of 2,6-dimethyl-5-heptenal to justify its use as an analog for heptanal. The 90-day feeding study that used C8-C12 aldehydes mixture as an analog for octanal and nonanal is inadequate because the study was conducted using a single concentration that was a NOAEL.

The reliability code for the 90-day data has been changed to "not reliable" to reflect EPAs comments.

Reproductive/Developmental Toxicity. For the reproductive/developmental toxicity endpoint, the adequate studies on heptanoic acid and nonanoic acid are supported by a number of less reliable studies and support the conclusions of the submitter. EPA agrees with the submitter that based on the rapid metabolism of an aldehyde to an acid, the existing studies on acids appear to be appropriate for characterizing the developmental effects of the aldehydes in this category.

Ecological Effects *(fish, daphnid, and algal toxicity)*

The predicted ECOSAR values for acute toxicity to fish, daphnia, and algae were provided to support the measured data for each of these endpoints. Using SAR to support measured data in this manner is appropriate and consistent with the HPV Challenge guidance for applying structure-activity relationships (http://www.epa.gov/chemrtk/sarfinl1.htm).

The C7-C9 Consortium has sponsored algal and invertebrate toxicity studies for heptanal and nonanal. These data are included in the robust summaries and test

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SPECIFIC COMMENTS ON THE ROBUST SUMMARIES

General In the robust summaries, the wording of the substance name/analog is unclear and listing of CAS numbers is also inconsistent. In some cases, the CAS number is that of the analog, but in other cases it is that of the category member. It would be preferable to list the CAS number of the analog and use the analog name as the Substance Name (with the category member in parentheses). For example:

Substance Name Octanoic acid (analog for heptanoic acid)
CAS No. 124-07-2

The robust summaries are revised to reflect the recommendations of EPA. The analog will be identified by the substance name.

Health Effects

In many cases, the robust summaries did not provide complete details for the methods and results, thus limiting the ability to allow an independent assessment of the quality of each study. The summaries for acute studies were commonly missing information on dose levels and test substance purity, and in one acute oral summary, no units were given for the LD50 value. The robust summaries for genetic toxicity studies sometimes lacked descriptions of positive controls, test concentrations, statistical methods, and test systems. Although the repeated dose study summaries provided more information, statistical methods and test substance purity descriptions were often missing. The summaries for reproductive and developmental studies provided sufficient information with the exception of test substance purity details.

If the details were included in the original studies, the data will be included in the robust summaries.

Environmental Effects

In general, the robust summaries were well prepared and presented the information necessary to understand the study design and results. However, some data elements such as water temperature, total organic carbon content, and dissolved oxygen demand were missing from the summaries. EPA has provided specific comments on how to enhance the robust summaries to the standard established in EPA's HPV Challenge Program Guidance at http://www.epa.gov/chemrtk/guidocs.htm.